From:	Kenny Crump
Reply To:	KennyCrump@email.com
To:	Ravi Subramaniam/DC/USEPA/US@EPA
Subject:	RE: your thoughts on utility of letter to editor re: recent BBDR paper
Date:	08/13/2010 05:14 PM

Ravi,

You give me far too much credit in claiming that I have gone through the paper in detail. In fact I haven't (and am not sure that I want to). I wasn't really aware of the role of BD when I made my comments. And doesn't equation 2 provide a discontinuity in their model. Any dose, no matter how inconsequential causes to death rate to jump to a different value. That doesn't make sense.

Perhaps my thinking in my comment was too simplistic. Yes, it does seem to me that BD should be chemical independent under their hypothesis. And yes, I would think that a wide range of parameters could provide the same fits due to the non-identifiability, so no meaning should be ascribed to the specific values of the parameters. I note that kdam for CHCL3 was not optimized. And that chemical seems to be the outlier. If it has been optimized, would the differences have gone away?

And yes, you are right, I am not feeling that I have the energy or desire to get into this. It is a different issue that what we have been addressing up to now. At least they did not propose low dose risk estimation using their model. Making too much of this might make it seem that we are crusading against Conolly himself. However, if the paper gained acceptance and was used to drive policy, that would be a different matter.

Regards,

Kenny

Kenny S. Crump
Louisiana Tech
P.O. Box 10348
Ruston, LA 71272-0046
Direct Dial: 318-257-4051
Cell: 318-278-9426
FAX: 318-257-2182
KennyCrump@email.com
Web Page: http://www2.latech.edu/~kcrump/

Home:
Kenny and Shirley Crump
2220 S. Vienna
Ruston, LA 71270

318-255-7058

From: Subramaniam.Ravi@epamail.epa.gov [mailto:Subramaniam.Ravi@epamail.epa.gov]
Sent: Friday, August 13, 2010 2:27 PM
To: KennyCrump@email.com
Cc: White.Paul@epamail.epa.gov
Subject: RE: your thoughts on utility of letter to editor re: recent BBDR paper

Kenny

Thanks for going through it in detail. For the purpose of the hypothesis here, your idea of plotting tumor response against alpha_n seems very good and a much better approach than going through the 2-stage model. Yes, it looks like N and Nctrl should be reversed.

I dont understand the second para of your comment. If the parameters are not identifiable, then how does one separate the chemical specific parameters from those that the MOA hypothesis says should be independent of the chemical? They needed to vary both k_dam (stated to be chemical specific) and BD in order to fit to the data. And in the case of one chemical they could not uniquely estimate k_dam. So, presumably, at least for this chemical, different values of BD could be used (depending on what value they came up with for k_dam).

Likewise, they could not uniquely identify the mutation and BD parameters. So they arbitrarily decided they would fix one (the mutation-related) and vary the BD parameters. The conclusions in the paper are entirely dependent on the fact that BD is different across chemicals. If they had decided to fix BD and vary the other, would they have arrived at the same conclusions? And, except for the cell replication rates I doubt if other parameters can be given the "biological" meaning that has been ascribed to them. . . I really dont see the utility of this biological model (or the bar that has been set here) for MOA purposes.

I sense that you are not too keen on a letter to the editor on this paper. Am I right in reading between the lines? My energy for such an action also dropped soon after I send my note out to you all.

Ravi.

Ravi Subramaniam
Environmental Health Scientist
NCEA-Washington, ORD, EPA
N-7922, Two Potomac Yard, Crystal City
(703) 347-8606, (301) 515-2701 (alternate office)

From:	"Kenny Crump" <KennyCrump@email.com>
To:	Ravi Subramaniam/DC/USEPA/US@EPA
Date:	08/11/2010 11:55 AM
Subject:	RE: your thoughts on utility of letter to editor re: recent BBDR paper

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Ravi,

I understand the paper a little better now, but not completely. My interpretation of their hypothesis is that the tumor response is determined by the cell damage. So for the same amount of cell damage the tumor response would be same, regardless of the chemical. It seems to me that this could best be examined by simply plotting the tumor responses in the various studies on the same graph as a function of damage as represented by aN which is the only input to the two stage model. The two-stage model just seems to obfuscate. I haven't really studied their computation of aN.

Having said that, I guess I don't see the fact that they are modeling only one time point as terribly important. Yes, the parameters will not be identifiable. But the important thing for their hypothesis is whether the same set of parameters predict the tumor responses in all three chemicals.

Just from a very cursory look at their equations, I found the following: Eq. (A13) expresses the cell division rate as a function of the control rate, the maximal rate and the ratio of the number of liver cells N to the control number. Since the maximal rate is 1000 times larger than the background rate, aN decreases extremely rapidly with any increase in N and will be negative for essentially any N greater than the control value. This doesn't make sense. Perhaps this is just a typo, as it would make sense if the N and Nctrl are reversed.

Regards,

Kenny

Kenny S. Crump
Louisiana Tech
P.O. Box 10348
Ruston, LA 71272-0046
Direct Dial: 318-257-4051
Cell: 318-278-9426
FAX: 318-257-2182
KennyCrump@email.com
Web Page: http://www2.latech.edu/~kcrump/

Home:
Kenny and Shirley Crump
2220 S. Vienna
Ruston, LA 71270
318-255-7058

-----Original Message-----
From: Subramaniam.Ravi@epamail.epa.gov
[mailto:Subramaniam.Ravi@epamail.epa.gov]
Sent: Tuesday, August 10, 2010 3:42 PM
To: KennyCrump@email.com
Subject: RE: your thoughts on utility of letter to editor re: recent BBDR paper

I missed the first part of your question in my last email. The bottom of the paper is the first complete paragraph on page 262 second column, starting with "The hypothesis that . . . "

In their fits they found that the parameter (BD) for the factor by which I cell death rate was reduced upon exposure (from that of normal cells) was significantly different for each chemical. So they inferred that cytotoxicity driven regenerative cell proliferation alone could not explain differences in tumor incidences across the chemicals (which had been hypothesized to share the same MOA).

Ravi.

Ravi Subramaniam
Environmental Health Scientist
NCEA-Washington, ORD, EPA
N-7922, Two Potomac Yard, Crystal City
(703) 347-8606, (301) 515-2701 (alternate office)

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From: "Kenny Crump" <KennyCrump@email.com>

To: Ravi Subramaniam/DC/USEPA/US@EPA

Date: 08/10/2010 03:51 PM

Subject: RE: your thoughts on utility of letter to editor re: recent BBDR paper

Hi Ravi,

I am not sure if I am up to evaluating another of Rory's BBDR papers. On first look, I am having trouble seeing the bottom line, or even finding the tumor data they used. Can you guide me?

Kenny

Kenny S. Crump
Louisiana Tech
P.O. Box 10348
Ruston, LA 71272-0046
Direct Dial: 318-257-4051
Cell: 318-278-9426
FAX: 318-257-2182
KennyCrump@email.com
Web Page: http://www2.latech.edu/~kcrump/

Home:
Kenny and Shirley Crump
2220 S. Vienna
Ruston, LA 71270
318-255-7058

-----Original Message-----
From: Subramaniam.Ravi@epamail.epa.gov [mailto:Subramaniam.Ravi@epamail.epa.gov]
Sent: Tuesday, August 10, 2010 12:19 PM
To: KennyCrump@email.com; Chiu.Weihsueh@epamail.epa.gov; White.Paul@epamail.epa.gov; Chen.Chao@epamail.epa.gov; Guyton.Kate@epamail.epa.gov
Subject: your thoughts on utility of letter to editor re: recent BBDR paper

Hi All:

Here is a paper (an effort I believe largely by Hisham and Rory) that has just been published which claims to be a demonstration of using BBDR modeling for risk assessment, specifically to inform MOA considerations. It is fundamentally flawed on many accounts. For example, tumor data to

which the 2-stage model is fit is available for only one time point and
a
critical parameter, the delay constant, has been used from Rory's
formaldehyde paper. The chemicals for which it has been applied have
nothing
to do with formaldehyde.

I am attaching the paper and my reviews of this paper and would
appreciate
hearing from you as to the merits or de-merits (including political
ones) of
writing a letter to the editor critiquing it.

Please keep this email to yourself.
(See attached file: Luke et al BBDR 2010.pdf)(See attached file:
Review_Luke_BBDRms_firstsubmission.doc)(See attached file:
Review_Luke_BBDR_revised.doc)

Ravi.

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Ravi Subramaniam
Environmental Health Scientist
NCEA-Washington, ORD, EPA
N-7922, Two Potomac Yard, Crystal City
(703) 347-8606, (301) 515-2701 (alternate office)

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